



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

07.03.04

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03078201.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

BEST AVAILABLE COPY



PCT/EP2004/011387

07.10.04

Anmeldung Nr:
Application no.: 03078201.5
Demande no:

Anmeldetag:
Date of filing: 10.10.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

DSM IP Assets B.V.
Het Overloon 1
6411 TE Heerlen
PAYS-BAS

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Activated carbon treatment

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

B01D39/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

ACTIVATED CARBON TREATMENT

The present invention relates to a process for purification of a compound by using activated carbon treatment.

Since decades, in processes for purifying valuable compounds, activated carbon treatments are applied wherein bulk activated carbon powder is used for removal of impurities such as coloured species from the valuable compound. However, the problem when using bulk carbon powder is that often activated carbon particles migrate downstream resulting in carbon contamination in subsequent recovery steps. Also, working with bulk carbon in industrial scale purification processes does not benefit health and safety. More recently, activated carbon cartridges have been developed that overcome these problems. In these cartridges, activated carbon is immobilised in a filtration medium. The use of an activated carbon cartridge is described for purification of penicillin V (R. Jansson and M. Weaver, Manufacturing chemist, march 2002, p. 29-30). However, despite the fact that the use of carbon cartridges also removes time consuming recovery processes and leads to an improved quality of the final product, the cartridges have not been widely implemented in industrial processes, despite the long felt need for an improvement of conventional carbon treatment.

One of the problems is that the yield of the desired compound is not always favourable enough to run the purification with activated carbon cartridges at a commercially efficient industrial scale.

The object of the present invention is to overcome this problem of insufficient yield of the desired compound. This problem is solved by the present invention wherein a feed containing the compound is passed over a first series of n connected filter units operating in series and wherein n is at least two and said filter units having been assigned a position number 1 to n in the series and wherein position number 1 is the first supplied with the feed; and subsequently a filter unit is disconnected from this first series at any position number between 1 to $n-1$ and an additional filter unit is connected at any position number that has a higher number than the position number of the disconnected filter unit, resulting in a second series of filter units; and subsequently the feed comprising the compound is passed over the second series of filter units

The present invention therefore relates to a process for purification of a compound, said process comprising an activated carbon treatment using a filter unit

containing activated carbon immobilized in a matrix, as is state of the art, characterized in that the process comprises the steps of

- a) passing a feed containing the compound over n connected filter units operating in series and wherein n is at least two and said filter units having been assigned a position number 1 to n in the series and wherein position number 1 is the first supplied with feed,
- b) disconnecting a filter unit from the first series at any position number between 1 to $n-1$, and connecting an additional filter unit at any position number that has a higher number than the position number of the disconnected filter unit, resulting in a second series of filter units,
- c) passing the feed containing the compound over the second series of filter units.

Use of carbon treatment in accordance with the present invention results in increased yield of the purified compound. Also, use of carbon treatment in accordance with the present invention results a complete utilization of available adsorption capacity of activated carbon. Furthermore, application of the activated carbon treatment according to the present invention provides a high throughput purification system. High throughput implies shorter processing times and improved logistics. This results in increased capacity to produce more valuable compound at an industrial scale. Preferably, in processes for purification of an instable compound, the yield of the purified compound is increased.

In the present invention, the compound may be an instable compound. The compound may comprise secondary metabolites or enzymes or their precursors. Secondary metabolites may comprise antibiotics, vitamins, carotenoids or polyunsaturated fatty acids (PUFAs). Enzymes may comprise natamycin, lactase, fromase, cytolase, invertase or endoxylanase. The antibiotic may comprise streptomycin, chloramphenicol, actinomycin, tetracycline, clavulanic acid, penicillin-G, penicillin-V, 6-aminopenicillanic acid (6-APA), 7-aminodeacetoxy cephalosporinic acid (7-ADCA), 7-aminocephalosporanic acid (7-ACA), semisynthetic penicillins such as amoxicillin, cloxacillin, flucloxacillin, methicillin, oxacillin, carbenicillin, or ampicillin and semisynthetic cephalosporins such as sephalexin, cephadrin, cephaloridine, cephalothin, cefaclor, cefadroxil. The carotenoids may comprise β -carotene.

In a particular aspect of the present invention, the compound is produced by fermentation using a micro-organism. The micro-organism may be prokaryotic or eukaryotic or cell or cell lines of mammalian or plant origin that is capable of producing a compound of interest during fermentation. Preferably, the micro-organism is a bacteria,
5 a fungus or a yeast. The bacteria may be an *E.coli*, *Streptomyces*, *Bacillus* or *Propionibacterium* strain. The Fungus may be a *Penicillium*, *Aspergillus* or *Mucor* strain. The yeast may be a *Saccharomyces*, *Kluyveromyces* or *Pichia* strain.

In a preferred embodiment of the present invention, the compound is obtained by fermentation using as micro-organism a *Streptomyces* species. Compounds obtained by
10 fermentation of *Streptomyces* species are particular suitable to be purified using the carbon treatment according to the present invention since a raw extract comprising *Streptomyces* species and the produced compound also contains a specific coloring species and other impurities that may notably be manifested by a yellow-to-red/brown color and that according to the present invention are very efficiently removed from the
15 compound with a surprisingly high yield of the purified compound. Preferred *Streptomyces* species may be *Streptomyces clavuligerus*, *S. coelicolor*, *S. griseus*, *S. Venezuela*, *S. aureofaciens*. The compounds produced by these strains may be clavulanic acid, streptomycin, chloramphenicol, tetracycline, actinomycin or beta carotene. Preferably, the compound is clavulanic acid.

20 The compound according to the present invention may be isolated from the fermentation broth by filtration. Subsequently, the compound may be precipitated or purified using other techniques known in the art, prior to the treatment with activated carbon. The feed that is subjected to the activated carbon treatment according to the present invention contains the compound and includes a solvent. The solvent may be
25 water, an alcohol, a keton, an ester, an ether or a mixture thereof. Preferably it comprises an ester like alkylacetate, more preferably (m)ethylacetate.

The filter units contain activated carbon immobilized in a matrix. The matrix may
be any porous filter medium permeable for the feed containing the compound.

30 Preferably, the matrix comprises a support material and/or a binder material. The support material in the matrix may be a synthetic polymer or a polymer of natural origin. The synthetic polymer includes polystyrene, polyacrylamide, polymethyl methacrylate. The polymer of natural origin includes cellulose, polysaccharide, dextran and agarose. Preferably the polymer support material is in the form of a fibre network to provide

sufficient mechanical rigidity. The binder material may be a resin. The matrix may have the form of a membrane sheet. Preferably, the activated carbon immobilized in a matrix may be in the form of a cartridge. A cartridge is a self-containing and readily replaceable entity containing powdered activated carbon immobilized in the matrix and prepared in the form of a membrane sheet. The membrane sheet may be captured in a plastic permeable support to form a disc. Alternatively, the membrane sheet may be spirally wounded. To increase surface area, several discs may be stacked upon each other. Preferably, the discs stacked upon each other have a central core pipe for collecting and removal of the carbon-treated feed from the filter unit. The configuration of stacked discs may be lenticular.

Carbon may be used from different sources of raw material such as peat, lignite, wood or coconut shell. The choice of carbon source depends on the compound to be isolated and may be determined according to methods known in the art. Carbon may be activated by processes known in the art such as by steam-treatment or chemical-treatment.

In the present invention, the activated carbon immobilized in a matrix may be placed in a housing to form an independent filter-unit. Each filter-unit has its own in-let and out-let for the feed containing the compound to be purified.

In the purification process according to present invention, the activated carbon treatment is carried out using a filter unit containing activated carbon immobilized in a matrix, characterized in that the process comprises the steps of

- a) passing a feed containing the compound over a first series of n connected filter units operating in series and wherein n is at least two and said filter units having assigned a position number 1 to n in the series and wherein position number 1 is the first supplied with feed,
- b) disconnecting a filter unit from the first series of filter units at any position number between 1 to $n-1$, and connecting an additional filter unit at any position number that has a higher number than the position number of the disconnected filter unit, resulting in a second series of filter units
- c) passing the feed containing the compound over the second series of filter units

In a preferred embodiment of the present invention, a filter unit may be disconnected at position number 1 and an additional filter unit may be connected at position number $n+1$.

5 In the process according to the present invention a feed containing the compound is passed over at least 2 connected filter units operating in series. Preferably $n=2$ to 10. More preferably, $n=2$ to 4, most preferably $n=3$. Also, several filter-units operating in series may additionally be connected in parallel in order to process large streams of feed comprising the compound to be purified.

10 In one particular aspect of the invention, wherein a series of 2 connected filter units is used, the filter unit in position number one, i.e. at the head of the series, is supplied with a feed containing the compound to be purified and the effluent of this filter unit one is passed over a second filter unit in position number 2. When a certain volume of feed has passed through the filter units, a switch in use of the filter units is made by disconnecting the filter unit in position number 1 and connecting an additional filter unit
15 in position number 3 and resulting in a renumbering of the position numbers since the filter unit original at position number 2 is now first supplied with feed and assigned position number 1 and the filter unit previously in position number 3 is now assigned position number 2.

20 In another aspect of the invention, when a series of 3 connected filter units is used, the filter unit in position number one, i.e. at the head of the series, is supplied with the feed containing the compound to be purified and the effluent of this filter unit one is passed over a second filter-unit in position number 2 and the effluent of this filter unit two is passed over a third filter unit in position number 3. When a certain volume of feed has passed through the three filter units, a switch in use of the filter units is made by
25 disconnecting the filter unit in position number 1 and connecting an additional filter unit in position number 4 resulting in a subsequent renumbering of the position numbers since the filter unit original at position number 2 is now first supplied with feed and assigned position number 1 and the filter unit previously in position number 3 is now
30 assigned position number 2 and the additional filter unit connected at position-number-4 is now assigned position number 3. Alternatively, instead of disconnection of the first filter unit, the second one (i.e. in position number 2) may be disconnected, resulting in that the filter unit in position number 1 remains here since it is still first supplied with feed and the filter unit in position number 3 is now assigned position number 2 and the

additional filter unit connected at position number 4 is assigned position number 3 in the second series.

The filter unit disconnected from the series is a filter unit that contains used activated carbon i.e. feed containing the compound to be purified has been passed over this activated carbon. The additional filter unit that is connected to the series is a filter unit that may contain un-used activated carbon (i.e. fresh carbon) or it may contain regenerated activated carbon.

In the process according to the present invention, each filter-unit may be connected and disconnected from the series of filter units by physical movement of the unit. Preferably, the filter unit may be connected and disconnected from the series of filter units without physical movement of the unit. This may be facilitated by a flow distribution system. This flow distribution system may be fully automated. Preferably, the flow distribution system may comprise multi-functional and multi-port valves preferably of the block-and-bleed type. The operation of said valves may be controlled by software. More preferably, connection and disconnection of filter units takes place simultaneous.

In the present invention, the process may be operated in batch, semi-continuous or continuous mode. With operation in batch mode is meant passing an amount of feed over the connected filter-units operating in series and said feed is terminated at the moment a filter-unit is disconnected and/or an additional filter unit is connected to the series. Subsequently, after the disconnection and connection has taken place, the flow of feed is continued. With operation in semi-continuous mode is meant passing an amount of feed over the connected filter-units operating in series and continuing said feed (i.e. the feed is not terminated) at the moment a filter unit is disconnected or an additional filter unit is connected and said feed is terminated at the moment the activated carbon immobilized in a matrix present in a filter unit is replaced. With operation in continuous mode is meant a process wherein an amount of feed is passed over the connected filter-units operating in series and the passing of the feed is continued (i.e. not terminated) at the moment a filter unit is disconnected or an additional filter unit is connected and the passing of the feed is continued over the additional filter unit when the activated carbon immobilized in a matrix is replaced in the filter unit that is disconnected.

The process according to the present invention can be carried out in a variety of embodiments, all aiming to increased yield of the compound.

In a first embodiment, the flow rate of the feed is 0.05 to 400 L/min, preferably 20 to 100 L/min, more preferably 30 to 40 L/min of the activated carbon. This may be accomplished by rinsing with a solvent according to processes known in the art. Typical solvents for regeneration may be min. The flow rate of the feed is at least 0.05 L/min. Preferably the flow rate is at least 20 L/min, more preferably the flow rate is at least 30 L/min. The flow rate may have a maximum of 400 L/min. Preferably the flow rate is not above 100 L/min, more preferably, the flow rate is not above 40 L/min.

In yet another embodiment, when the activated carbon immobilized in a matrix is in the form of a membrane sheet with surface area given in square meters (m^2), the flux of the feed is 1 to 50 $L/m^2/min.$, preferably 1.5 to 20 $L/m^2/min.$, most preferably 1.5 to 10 $L/m^2/min.$ Preferably, the flux is at least 1 $L/m^2/min.$ More preferably, the flux is at least 1.5 $L/m^2/min.$ The flux may have a maximum of 50 $L/m^2/min.$, preferably the flux is not above 20 $L/m^2/min.$, more preferably the flux is not above 15 $L/m^2/min.$ With flux is meant the flow rate of the feed per square metre of the surface area of the membrane sheet.

In yet another embodiment, the residence time of the feed containing the compound in a single filter unit is at least 15 seconds and maximal 60 minutes. The residence time of the feed containing the compound in a single filter unit is at least 15 s, preferably it is at least 30 s, more preferably it is at least 60 s, most preferably it is 2 min. The residence time of the compound in a single filter unit is maximal 60 min, preferably it is not more than 30 min, more preferably it is not more than 15 min. The residence time of the feed containing the compound in a single filter unit can be determined by measuring the difference in time between feed_{in} and feed_{out} over a single filter unit. When a feed containing the compound is passed over n connected filter units in series, the total residence time of the feed in the series is n times the residence time in a single filter unit.

In yet another embodiment, the process may be operated at a temperature between minus 10 to +40°C. It may be clear that the temperature is chosen in a way that the feed containing the compound is in the liquid phase both before and after passing it over the filter-units. The temperature may be dependent on the type of solvent present in the feed, and the thermo-stability of the compound. The temperature is at least minus 10 °C, preferably it is at least minus 2°C, more preferable it is at least 5°C. The

temperature may be not more than 40°C, preferably it is not more than 25°C, more preferably it is not more than 15 °C.

In yet another aspect of the present invention, the purification process is carried
5 out in a series of filter-units operated in series and wherein the activated carbon
immobilized in a matrix of at least one filter unit that is disconnected from the series is
regenerated "*in situ*" by rinsing preferably with a solvent.

With regeneration is meant recovery of the adsorption capacity methanol,
ethanol, acetone or ethylacetate. Regeneration may occur "*in situ*". With "*in situ*" is meant
10 that the filter-unit containing the activated carbon that is regenerated is rinsed with a
solvent without the need to physically move the filter-unit from its position in the series or
to physically move the activated carbon from the filter unit. During regeneration the
activated carbon may be subjected to the operations of rinsing with the solvent present
in the previous feed, and/or rinsing with the regeneration solvent, and/or wetting with the
15 solvent present in the next feed. In between the operations of rinsing and wetting the
activated carbon may be purged with a gas, preferably a nitrogen gas.

After applying the activated carbon treatment according to the present invention,
the compound may be further converted into a pharmaceutically acceptable salt or food
20 grade product according to processes known to a person skilled in the art.

Example 1

An aqueous broth of clavulanic acid obtained by fermentation was filtered, extracted and concentrated to 30 g/l prior to activated carbon treatment. 500 ml of concentrated extract was added to a beaker containing 50 g of bulk powdered activated carbon and magnetic stirrer. After a reaction time of 90 minutes, activated carbon was separated from the extract by using a Buchner funnel. The percentage decolourisation was determined by measurement of differences in extinction of the extract before and after activated carbon treatment on a colorimeter. Percentage decolourisation was 90%. Yield of clavulanic acid after activated carbon treatment was 86%.

Example 2

A fermentative obtained aqueous broth of clavulanic acid was filtered, extracted and concentrated to 30 g/l prior to activated carbon treatment. 500 ml of the concentrated extract was passed over a single filter unit containing an activated carbon filter plate (Zetacarbon® R35, ø90 mm from CUNO Ltd.) with approximate effective surface area of 0,0057 m². Flow of the feed with concentrated extract over the filter unit was set at 0.03 L/min. Flux was 5,0 L/min/m². Percentage decolourisation was 90%. Yield of clavulanic acid after carbon treatment was 90%.

Example 3

A feed of 37.5 litres containing concentrated clavulanic acid extract (25 g/L) is passed over 3 connected filter units operating in series, each filter unit containing fresh activated carbon cartridges (Zetacarbon® C08DB; R35S from CUNO Ltd.) with approximately 0.29 m² of effective surface area. The flow rate of the feed was 1.0 L/min. and the flux was 3.5 L/min./ m². The filter unit in position number 1 is first supplied with feed containing the impure extract. The filter unit in position number 2 is exposed to the effluent from filter unit 1. The Filter unit in position number 3 is exposed to the effluent from filter unit 2. A fourth additional filter unit is lined up in the series at position number 4 but not in service since it is not connected to the series of 3 filter units. After passing the 37.5 litres of extract over the 3 filter units, the filter unit number 1 that is first supplied with feed is disconnected from the series and an additional filter unit previously in position number 4 is connected to the series resulting in new assignment of position numbers: the unit previously in position number 4 is now assigned position number 3; the unit previously in position number 3 is now assigned position number 2; the unit

previously in position number 2 is now assigned position number 1 to form a second series of 3 connected filter units operating in series whereof the first and second one in the series are both once used and the third filter unit in the series is fresh. After disconnecting a filter unit and connecting an additional filter, the feed was continued and by passing 37.5 of non-carbon treated litres containing concentrated clavulanic acid extract over this second series of 3 connected filter units. In this second filtration the decolourisation percentage was 94%. Total yield of clavulanic acid was 94%.

Example 4

The activated carbon treatment of example 3 was repeated with the following difference: The filter units in both the first and the second series of 3 connected filter units contained respectively a twice used cartridge at position number 1, an once used cartridge at position number 2 and a fresh cartridge at position number 3. In the second filtration the decolourisation percentage was 93%. The yield of clavulanic acid in the total collected decolourised extract was 97%.

Example 5

The activated carbon treatment was carried out according to example 4. After passing the feed with clavulanic acid over the second series of filter units, the activated carbon cartridges contained in the filter units were washed by passing 21 l of ethylacetate over the filter units. The decolourisation percentage was 94%. The yield of the total collected decolourised extract was 98%.

CLAIMS

1. Process for purification of a compound, said process comprising an activated carbon treatment using a filter unit containing activated carbon immobilized in a matrix, characterized in that the process comprises the steps of
 - a. passing a feed containing the compound over a series of n connected filter units operating in series and wherein n is at least two and said filter units having been assigned a position number 1 to n in the series and wherein position number 1 is the first supplied with feed,
 - b. disconnecting a filter unit from the first series of filter units at any position number between 1 to $n-1$, and connecting an additional filter unit at any position number that has a higher number than the position number of the disconnected filter unit, resulting in a second series of filter units, and
 - c. passing the feed containing the compound over the second series of filter units.
2. The process according to claim 1, wherein the filter unit is disconnected at position number between 1 to $n-1$ and wherein the additional filter unit is connected at position number $n+1$.
3. The process according to claim 1, wherein the filter unit is disconnected at position number 1 and wherein the additional filter unit is connected at position number $n+1$.
4. The process according to any of claims 1 to 3 wherein the number of connected filter units operating in series $n=2$ to 10.
5. The process according to any of claims 1 to 4, wherein the process is operated in batch, semi-continuous or continuous mode.
6. The process according to any of claims 1 to 5, wherein the flow rate of the feed is 0.05 to 400 L/min, preferably 20 to 100 L/min, more preferably 30 to 40 L/min.

7. The process according to any of claims 1 to 6 wherein the activated carbon immobilized in a matrix is in the form of a membrane sheet .
- 5 8. The process according to claim 7, wherein the flux over the membrane sheet is 1 to 50 L/m²/min. , preferably 1.5 to 20 L/m²/min., most preferably 1.5 to 10 L/m²/min.
- 10 9. The process according to any of claims 1 to 8, wherein the residence time of the feed containing the compound in a single filter unit is at least 15 seconds and maximal 60 minutes.
- 15 10. The process according to any of claims 1 to 9, wherein the temperature is between minus10 °C to 40°C.
- 20 11. The process according to any of claim 1 to 10, wherein at least one filter unit is regenerated *in situ* by rinsing with a solvent.
- 25 12. The process according to any of claims 1 to 11, wherein the compound is an instable compound.
- 30 13. The process according to claim 12, wherein the instable compound is a secondary metabolite or an enzyme.
14. The process according to claim 13, wherein the secondary metabolite is selected from the group consisting of an antibiotic, a vitamin, a carotenoid or a PUFA.
15. The process according to any of claims 1 to 11, wherein the compound is obtained by fermentation using a microorganism.
16. The process according to claim 14, wherein the microorganism is a *Streptomyces* species.

17. The process according to claim 15, wherein the *Streptomyces* species is selected from the group consisting of *S. clavuligerus*, *S. coelicolor*, *S. griseus*, *S. Venezuela*, *S. jumonjinensis*, *S. katsurahamanus* or *S. aureofaciens*.
- 5 18. The process according to claim 15 or 16, wherein the compound is selected from the group consisting of clavulanic acid, streptomycin, chloramphenicol, tetracycline or β -carotene.
- 10 19. The process according to any of the previous claims, further comprising the step of converting the compound into a pharmaceutically acceptable salt or food grade product.

ACTIVATED CARBON TREATMENT**ABSTRACT**

5 Present invention relates to a process for purification of a compound using an
activated carbon treatment. In the process according to the present invention several
filter units containing activated carbon immobilized in a matrix are operating in
series, and after passing an amount of feed, a filter unit from this first series of filter
units is disconnected at a particular position number, and an additional filter unit is
10 connected at another particular position number herewith obtaining a second series
of filter units where over the passing of the feed is continued.

This process overcomes the problem of loss of yield of the purified compound as
occurs during conventional activated carbon treatment.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP04/011387

International filing date: 07 October 2004 (07.10.2004)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 03078201.5
Filing date: 10 October 2003 (10.10.2003)

Date of receipt at the International Bureau: 24 February 2005 (24.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.